173. The Chemistry of Drugs

Part IV[1])

Configurations of Antimalarials Derived from Qinghaosu: Dihydroqinghaosu, Artemether, and Artesunic Acid

by **Xuan-de Luo,**[2]) **Herman J.C. Yeh,** and **Arnold Brossi***

Laboratory of Chemistry, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20205, USA

and **Judith L. Flippen-Anderson** and **Richard Gilardi**

Laboratory of the Structure of Matter, Naval Research Laboratories, Washington, D.C., 20201, USA

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Summary

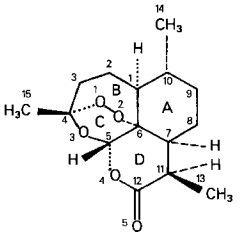
The structures of the antimalarials dihydroqinghaosu (**2**), artemether (**3**), and artesunic acid (**7a**) derived from qinghaosu were elaborated by ^{1}H-NMR spectroscopy, and supported with X-ray data obtained for **2** and **3.** Several new derivatives, useful for the chemical characterization of dihydroqinghaosu (**2**) and artesunic acid (**7a**), were prepared.

The prevention and treatment of malaria were confronted with great difficulties after the chloroquine-resistant parasite appeared in the early 1960's. Qinghaosu (**1;** qing hau sau), extracted from a traditional Chinese herb, is a new type of an antimalarial drug with rapid action and low toxicity. It has direct parasiticidal action on *Plasmodium* in the erythrocytic stage, and affects *Plasmodium falciparum,* the parasite responsible for tropical malaria, as well as *Plasmodium vivax* and chloroquine-resistant *falciparum malaria* [2]. The absolute configuration of qinghaosu, a sesquiterpene lactone with a peroxide bridge, first isolated in China from *Artemisia annua* L. [3] [4], was firmly established by X-ray diffraction [5], and later confirmed by total synthesis [6]. In parallel with the clinical evaluation of qinghaosu (**1**) in China are studies with the analogs artemether (**3**) and artesunate (the sodium salt of **7a**).

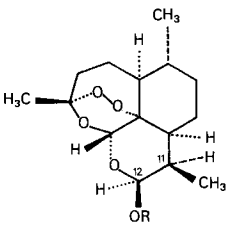
These analogs originate from dihydroqinghaosu (**2**), prepared from **1** by reduction with $NaBH_4$ in MeOH [4], a solvent where **2** exists as a mixture of α- and β-isomers. It was reported that the acid-catalyzed alkylation of **2** gave mainly the acetales with

[1]) Part III, see [1].

[2]) Guest worker from the Institute of Chinese Materia Medica, Academy of Traditional Chinese Medicine, Beijing, China, on a program sponsored by the *Special Program for Research and Training in Tropical Diseases* by *WHO,* Geneva.

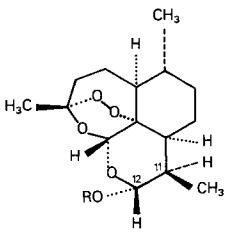


1 qinghaosu



β-series

2 R = H dihydroqinghaosu
3 R = CH_3, artemether
4 R = CD_3 deuteroartemether-I



α-series

5 R = CD_3, deuteroartemether-II
6 R = CONH–⬡–X
a X=H
b X=NO_2
7 R = CO–$(CH_2)_2$–COOX
a X=H
b X=CH_3
c X=CH_2–⬡–NO_2
8 R = CO–⬡–NO_2

[a]) Arbitrary numbering. For systematic numbering, *cf.* the names in the *Exper. Part.*

β-configuration, while acylation of **2** in alkaline medium led almost exclusively to α-configurated derivatives [7–9].

To obtain information on the configuration of crystalline **2** of m.p. 152–154°, and further data on its equilibrium in solution, a detailed ^{1}H-NMR study including compounds **2–8** was carried out (see discussion below).

The *O*-(D_3)methyl acetals **4** and **5** were prepared from **2** by an acid-catalyzed reaction with CD_3OD, followed by separation of the faster moving β-isomer from its slower moving α-isomer by chromatography on silica gel. The benzene carbamates **6a** and **6b** were obtained from **2** with phenyl isocyanates in refluxing CH_2Cl_2 solution. Esterification of artesunic acid (**7a**) with ethereal diazomethane afforded the methyl ester **7b**, and **7c** was obtained from **7a** with *p*-nitrobenzyl 8 reagent [10]. The *p*-nitrobenzoate **8** was obtained from **2** and *p*-nitrobenzoic acid in CH_2Cl_2 with *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine as a catalyst. All compounds, except **2, 4,** and **6a,** were amorphous solids, but their chemical purity was secured by TLC analysis combined with ^{1}H-NMR and mass spectroscopy. Both, **2** and **3,** afforded crystals suitable for X-ray analysis (see discussion below), confirming the configurational assignments obtained by ^{1}H-NMR analysis. Although it can be anticipated that derivatives of **2** and **7a** will be of little value for studying the metabolic fate of **2, 3,** or **7a,** they may be useful to assess the chemical purity and stability of formulations intended for clinical studies.

Results and Discussion of ^{1}H-NMR Data. – In the ^{1}H-NMR spectra ($CDCl_3$) of **2–8,** the assignments for the protons on ring D (except H–C(7)) and for the three CH_3-groups were straightforward.

Table 1. *Selected ^{1}H-NMR Data* ($CDCl_3$; 100 MHz) *of* **2–8**

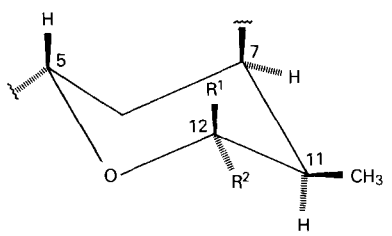
Compound	$\delta_{H-C(5)}$ [ppm]		$\delta_{H-C(12)}$ [ppm]		$\delta_{H-C(11)}$ [ppm]		$^3J_{11,12}$ [Hz]		$^3J_{7,11}$ [Hz]	
	α	β	α	β	α	β	α	β	α	β
2	(5.34)[a]	5.56	(4.71)[a]	5.26	(2.31)[a]	2.56	(9.2)[a]	3.1	–	–
3	–	5.35	–	4.65	–	2.57	–	3.4	–	4.3[b]
4	–	5.37	–	4.67	–	2.59	–	3.4	–	–
5	5.32	–	4.32	–	2.36	–	9.3	–	–	–
6a	5.49	–	5.78	–	2.62	–	9.8	–	–	–
6b	5.57	–	5.79	–	2.66	–	9.8	–	–	–
7a	5.40	–	5.77	–	2.56	–	9.8	–	4.3[b]	–
7b	5.42	–	5.79	–	2.54	–	9.8	–	–	–
7c	5.39	–	5.75	–	2.48	–	9.8	–	–	–
8	5.53	–	6.05	–	2.74	–	9.8	–	–	–

[a]) These data are derived from a spectrum containing both the α- and β-species after equilibration.
[b]) These values are obtained from spectra taken on a *Nicolet 500* NMR spectrometer.

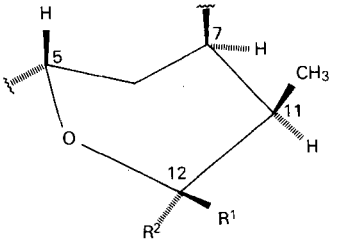
In **2–8**, the *s* at δ 5.3–5.6 was assigned to H–C(5), the *d* at δ 4.3–6.1 to H–C(12), and the *m* at δ 2.3–2.7 to H–C(11). *Table 1* lists the chemical shifts and coupling constants associated with these protons in **2–8**. The signals at δ 0.78–0.93 (*d*, J = 7.1–7.4 Hz, 3H), 0.92–0.97 (*d*, J = 6.0–6.4 Hz, 3H), and 1.31–1.43 (*s*, 3H), were assigned to the C(13), C(14) and C(15) methyl protons, respectively.

An assignment of the remaining protons in rings A–C is more difficult due to clustering of these signals in the range between δ 0.93–2.3. A complete analysis, however, was possible from spectra taken on a 500 MHz instrument. All the assignments mentioned were confirmed by double-resonance experiments.

Configurations and Conformations. – Each α- or β-isomer of **2** and its derivatives can exist in two conformations of ring D, a half-chair form **A** and a half-boat form **B.** The relative configurations at C(7), C(11), and C(12) is reflected by the $^3J_{7,11}$ and $^3J_{11,12}$ values based on *Dreiding* models and *Karplus* relation [11]. Since the absolute configuration of qinghaosu (**1**) was established by X-ray diffraction, the formulae shown for **2** and derived analogs also present absolute configurations.



A
α, R^1 = H, R^2 = OR
β, R^1 = OR, R^2 = H



B
β, R^1 = H, R^2 = OR
β, R^1 = OR, R^2 = H

Conformations of ring D in dihydroqinghaosu and derivatives

Table 2. *Values of Calculated Vicinal Coupling Constants, $^3J_{7,11}$ and $^3J_{11,12}$, Based on the Dihedral Bond Angles, ϕ(H–C(7),H–C(11)) and ϕ(H–C(11),H–C(12)), of the Four Possible Conformations of Ring D*

Conformation	ϕ(H–C(7),(H–C(11))	$^3J_{7,11}$	ϕ(H–C(11),H–C(12))	$^3J_{11,12}$
Aα	60°	2–6 Hz	170°	8–13 Hz
Aβ	60°	2–6 Hz	50°	2–7 Hz
Bα	20°	6–10 Hz	70°	1–4 Hz
Bβ	20°	6–10 Hz	50°	2–7 Hz

Using the *Dreiding* model, a set of vicinal coupling constants, $^3J_{7,11}$ and $^3J_{11,12}$, can be calculated for each of the four possible conformations based on projected dihedral bond angles. These values are listed in *Table 2*. It can be seen that the observed $^3J_{7,11}$ and $^3J_{11,12}$ values in **2–4** *(Table 1)* are in good agreement with one set of calculated values, corresponding to dihedral bond angles ϕ(H–C(7), H–C(11)) = 60° and ϕ(H–C(11),H–C(12)) = 50°, *i.e.* to the Aβ-conformation. For **5–8**, the observed *J*-values are only in good agreement with the set corresponding to the dihedral bond angles ϕ(H=C(7),H–C(11)) = 60° and ϕ(H–C(11),H–C(12)) = 170°, which is the Aα-conformation.

Therefore, **2–4** can confidently be assigned to the β-chair series in which the OR-group at C(12) is *cis* to the CH_3-group at C(11) and axially oriented on ring D. This assignment is in agreement with the X-ray results. Compounds **5–8** belong to the α-chair series with the OR-group at C(12) *trans* to the CH_3-group at C(11) and equatorially oriented on ring D.

$\alpha \rightarrow \beta$ Interconversion of 2. – Although the crystal of **2** used for the X-ray analysis exists solely in the β-configuration, an $\alpha \rightarrow \beta$ interconversion, presumably through an aldehyde-alcohol intermediate, was found to take place in solution. This was evident from the change in the ^{1}H-NMR spectrum that first showed the existence of the β-species and later of an α/β-isomeric mixture. The rate and equilibrium position of the $\alpha \rightarrow \beta$ interconversion are solvent dependent. For example, in $CDCl_3$, the equilibration takes about 8 h to reach a final α/β ratio of 1:1. But in CD_3OD, it requires only few min to reach a final α/β ratio of 2:1.

X-Ray Analysis and Discussion. – *X-Ray Crystallographic Data for Artemether* (**3**): $C_{16}H_{26}O_5$, mol. wt. 298.38, crystal size = 0.35 × 0.35 × 0.25 mm, monoclinic, space group $P2_1$, a = 9.868(7), b = 18.324(12), c = 10.172(7)Å, β = 117.55(5)°, V = 1630.7Å^3, Z = 4 (two molecules per asymmetric unit), d_{calc} = 1.22 g cm^{-3}.

The 2224 independent reflections were measured out to $2\theta_{max} = 45°$ with a computer-controlled diffractometer (*Nicolet R3*) at room temperature using MoK_α radiation with a graphite monochromator on the incident beam. The structure was solved by direct methods [12] [13] as implemented by the SHELXTL system of programs [14]. The two independent molecules in the asymmetric unit were found to have the same conformation. Full-matrix least-squares refinement using the 1432 reflections for which $|F_o| > 3\sigma_F$ gave a final R factor of 9.5% (R_w = 8.0%). The goodness of fit parameter was 1.3.

X-Ray Crystallographic Data for Dihydroqinghaosu (**2**): $C_{15}H_{24}O_5$, mol. wt. 284.35, crystal size = 0.05 × 1 × 0.4 mm, orthorhombic, space group $P2_12_12_1$, a = 5.659(3), b = 14.270(8), c = 18.954(8)Å, V = 1530.7Å^3, Z = 4, d_{calc} = 1.23 gcm^{-3}.

The 1989 independent reflections were measured under the same conditions as those used for crystal **3**. As for **3**, the structure was solved by direct methods and refined using full-matrix least-squares (1182 reflections for which $|F_o| > 3\sigma_F$). The final R-factor was 11.3% (R_w = 10.3%). The goodness of fit parameter was 1.6. Coordinates and thermal parameters for both molecules have been deposited with the *Crystallographic Data Centre*, Cambridge University, University Chemical Lab, Cambridge CB2 1EW, England.

The results of the X-ray studies on molecules **3** and **2** are illustrated in *Fig. 1* and *2*, respectively. Both compounds have the same relative conformation. The non-bridged 6-membered rings are both in a normal chair conformation while the 6-membered ring

formed by the O–O bridge has a somewhat distorted boat conformation. This conformation agrees with that found for quinghaosu [5]. In molecule **2**, there is an intermolecular H-bond formed between the OH-group and the ether O-atom (O(4)) in the ring of an adjacent molecule. The O...O distance is 2.79 Å. In molecule **3**, there are no intermolecular approaches less than *van der Waals* separations.

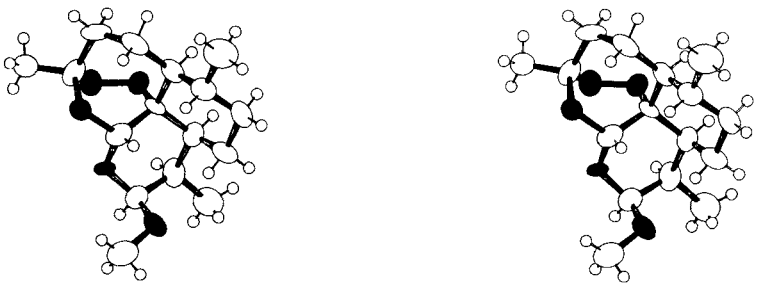


Fig. 1. *Structure and conformation of artemether* (**3**). The figure is drawn using the experimentally determined coordinates with arbitrary thermal parameters for the H-atoms. The O-atoms have been blackened for identification. The sample of **3** used for X-ray diffraction was crystallized from hexane, m.p. 86–7°, $[\alpha]_D^{25} = +163°$ ($c = 2.58$, $CHCl_3$).

Table 3. *Coordinates and* U_{eq} *Values for Artemether* (**3**)

Atom	x	y	z	U_{eq}
O(1a)	0.1851(8)	0.6363(4)	− 0.0975(8)	5.3(4)
O(2a)	0.0952(8)	0.7006(4)	− 0.1116(7)	4.6(4)
O(3a)	0.3751(8)	0.6591(4)	− 0.1399(8)	4.8(4)
O(4a)	0.4174(8)	0.7404(4)	− 0.0046(8)	4.8(4)
O(5a)	0.4824(8)	0.8642(5)	0.0238(9)	6.2(4)
C(1a)	0.1054(12)	0.7469(8)	0.1166(11)	5.4(6)
C(10a)	0.1444(14)	0.8127(7)	0.2236(13)	5.4(6)
C(9a)	0.1013(13)	0.8829(7)	0.1326(14)	6.5(7)
C(8a)	0.1867(14)	0.8908(8)	0.0404(14)	7.2(8)
C(7a)	0.1501(15)	0.8265(6)	− 0.0647(13)	5.2(6)
C(6a)	0.1771(11)	0.7512(7)	0.0066(11)	3.9(5)
C(5a)	0.3477(14)	0.7324(7)	0.0878(12)	5.6(6)
C(4a)	0.2532(13)	0.6107(6)	0.0493(10)	4.8(6)
C(3a)	0.1388(13)	0.6070(7)	0.1101(12)	6.0(6)
C(2a)	0.1391(13)	0.6742(7)	0.1980(12)	5.8(6)
C(11a)	0.2379(14)	0.8305(12)	− 0.1606(12)	6.1(7)
C(12a)	0.4025(13)	0.8081(7)	− 0.0746(13)	5.9(7)
C(13a)	0.2131(15)	0.9008(9)	− 0.2440(15)	8.8(9)
C(14a)	0.0685(17)	0.8069(10)	0.3241(14)	8.7(9)
C(15a)	0.3201(15)	0.5390(7)	0.0446(15)	7.1(8)
C(16a)	0.6440(14)	0.8501(8)	0.0979(16)	8.5(9)
O(1b)	0.4978(8)	0.3004(5)	0.4365(8)	5.6(4)
O(2b)	0.5088(8)	0.2311(5)	0.5129(8)	5.6(4)
O(3b)	0.2508(7)	0.2806(4)	0.2481(7)	4.3(3)
O(4b)	0.3988(8)	0.2062(4)	0.1957(8)	5.3(4)
O(5b)	0.3586(9)	0.0862(4)	0.1067(7)	5.8(4)
C(1b)	0.2726(14)	0.1822(7)	0.4998(12)	5.8(6)
C(10b)	0.1665(14)	0.1188(9)	0.4521(14)	6.5(7)

Table 3 (continued)

Atom	*x*	*y*	*z*	U_{eq}
C(9b)	0.2474(15)	0.0448(9)	0.4771(15)	7.2(8)
C(8b)	0.3404(12)	0.0453(6)	0.3882(12)	5.8(6)
C(7b)	0.4615(12)	0.1065(7)	0.4394(11)	4.9(6)
C(6b)	0.3827(12)	0.1812(6)	0.4192(11)	4.0(6)
C(5b)	0.3033(14)	0.2070(6)	0.2626(13)	5.8(7)
C(4b)	0.3419(13)	0.3242(7)	0.3736(11)	4.6(5)
C(3b)	0.2830(15)	0.3244(8)	0.4867(12)	7.2(7)
C(2b)	0.1913(15)	0.2559(8)	0.4808(14)	7.6(8)
C(11b)	0.5573(14)	0.1095(7)	0.3560(11)	5.3(6)
C(12b)	0.4660(14)	0.1380(7)	0.1938(11)	5.6(6)
C(13b)	0.6368(16)	0.0367(8)	0.3590(19)	9.9(10)
C(14b)	0.0710(16)	0.1189(10)	0.5367(15)	10.0(9)
C(15b)	0.3509(15)	0.3979(7)	0.3133(14)	7.5(8)
C(16b)	0.2914(14)	0.1049(7)	− 0.0437(11)	6.2(7)

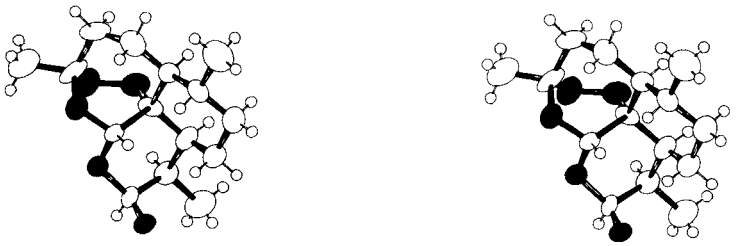


Fig. 2. *Structure and conformation of dihydroqinghaosu* (**2**). Drawn under the same conditions as that used for *Fig. 1*. The sample of **2** used for X-ray diffraction was crystallized from $(i\text{-Pr})_2O$, m.p. 152–4°, $[\alpha]_D^{22} = +129°$ ($c = 0.92$, $CHCl_3$).

Table 4. *Coordinates and* U_{eq} *Values for Dihydroqinghaosu* (**2**)

Atom	*x*	*y*	*z*	U_{eq}
O(1)	0.1581(11)	0.1306(4)	0.1287(3)	6.4(2)
O(2)	0.1437(9)	0.0453(4)	0.0846(3)	5.5(2)
O(3)	− 0.2367(11)	0.1454(4)	0.1467(3)	5.5(2)
O(4)	− 0.1837(11)	0.1881(4)	0.0332(3)	4.6(2)
O(5)	− 0.4099(10)	0.1564(4)	− 0.0682(3)	5.0(2)
C(1)	− 0.1786(17)	− 0.0605(6)	0.1103(4)	5.6(3)
C(10)	− 0.3913(18)	− 0.1133(6)	0.0819(5)	6.2(4)
C(9)	− 0.3687(22)	− 0.1362(6)	0.0030(5)	7.8(4)
C(8)	− 0.3101(20)	− 0.0483(6)	− 0.0401(4)	6.9(4)
C(7)	− 0.0896(16)	0.0000(6)	− 0.0145(4)	5.1(3)
C(6)	− 0.0997(14)	0.0256(6)	0.0655(4)	4.3(3)
C(5)	− 0.2510(16)	0.1099(5)	0.0767(4)	4.3(3)
C(4)	− 0.0249(15)	0.1259(7)	0.1799(4)	5.9(4)
C(3)	− 0.0262(24)	0.0320(7)	0.2188(4)	8.4(5)
C(2)	− 0.2075(19)	− 0.0361(7)	0.1887(4)	6.5(4)
C(11)	− 0.0171(18)	0.0880(7)	− 0.0572(4)	5.7(4)
C(12)	− 0.1821(20)	0.1702(6)	− 0.0419(4)	5.2(4)
C(13)	0.0075(24)	0.0706(8)	− 0.1366(4)	9.3(5)
C(14)	− 0.4594(29)	− 0.1994(7)	0.1249(6)	10.9(6)
C(15)	0.0370(29)	0.2098(8)	0.2273(5)	10.5(6)

Experimental Part

General Remarks. Melting points were taken on a *Fisher-Johns* melting point apparatus and uncorrected. Elemental analyses were performed by the section on Microanalytical Services and Instrumentation of this laboratory. Silica gel 60 (230–400 mesh ASTM) from *Merck* was used for column chromatography with a flash-chromatography column *(Aldrich Chemical Co.)*. Optical rotations were measured with a *Perkin-Elmer-241-MC* polarimeter in $CHCl_3$. UV spectra were measured in $CHCl_3$ with a *Hewlett-Packard-8450-A* spectrophotometer, $\lambda_{max}(\log \varepsilon)$ in nm. IR spectra (in cm^{-1}) were obtained on a *Beckman-4230* instrument as KBr tablet or $CHCl_3$ solution between NaCl plates. Chemical ionization (CI) mass spectra (m/z) were obtained by using a *Finnigan-1015D* spectrometer. ^{1}H-NMR spectra were determined by using a *JEOL-FX-100* spectrometer and a *Nicolet-500* spectrometer with Me_4Si as an internal reference (δ in ppm, J in Hz).

Thin Layer Chromatography. On silica gel *GF* (10 × 20 cm) from *Analtech, Inc.*, with petroleum ether/AcOEt 7:3 (A) or petroleum ether/AcOEt 6:4 (**B**); detection with iodine vapors or a 4% solution of vanillin in conc. H_2SO_4. R_f(**1**) 0.49–0.51 (A), 0.64–0.66 (**B**); R_f (**2**) 0.27–0.30 (A), 0.41–0.47 (**B**); R_f (**3**) 0.65–0.67 (A), 0.76–0.78 (**B**); R_f (**7a**) 0.01– = 0.02 (A), 0.03–0.05 (**B**); R_f (**7b**) 0.35–0.39 (A), 0.54–0.59 (**B**); all yellow with I_2; **1** blue and **2, 3, 7a,** and **7b** pink with vanillin.

Deuteroartemether-I (= *3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12a-dodecahydro-10β-(D)$_3$methoxy-3β,6α,9β-trimethylpyrano[4,3-j][1,2]benzodioxepin;* **4**) *and Deuteroartemether-II* (= *3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12a-dodecahydro-10α-(D$_3$)methoxy-3β,6α,9β-trimethylpyrano[4,3-j][1,2]benzodioxepin;* **5**). To a solution of dihydroqinghaosu (**2**; 284 mg, 1 mmol) in CD_3OD (2 ml) and dry benzene was added two drops of $BF_3 \cdot Et_2O$, and the mixture was set at r.t. for 23 h. The mixture was washed with sat. NaOAc and H_2O, dried with anh. Na_2SO_4 and filtered. The filtrate was evaporated under vacuum at 40° to give an oil, which was purified by column chromatography on silica gel with petroleum ether/AcOEt 8:2. On concentration of the first fractions, crystals gradually formed. Recrystallization from petroleum ether/AcOEt yielded **4** (224 mg), m.p. 85–86°, $[\alpha]_D^{27.5} = +155.10°$ (c = 1.0, $CHCl_3$). IR (KBr) 2925*s;* 2200*m*, 2055*m* (deuterium); 1016*s*, 845*m* (peroxide). ^{1}H-NMR: see *Table 1.* MS (CI; NH_3): 302 ($M^+ + 1$).

The second fractions obtained were combined and evaporated to give **5** as an oil (59.22 mg), $[\alpha]_D^{22.6} = 1.07°$($c$ = 1.6, $CHCl_3$). IR ($CHCl_3$): 2930*s*, 2875*s;* 2212*m*, 2060*m* (deuterium); 1010*s*, 868*m* (peroxide). ^{1}H-NMR: see *Table 1.* MS (CI; NH_3): 302 ($M^+ + 1$).

Dihydroqinghaosu-benzenecarbamate (= *3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12a-dodecahydro-3β,6α,3β-trimethylpyrano[4,3-j][1,2]benzodioxepin-10α-yl Benzenecarbamate;* **6a**). A solution of **2** (142 mg, 0.5 mmol) in CH_2Cl_2 (6 ml) and phenyl isocyanate (60 mg, 0.5 mmol) was refluxed for *ca.* 2 days. The solution was filtered and evaporated *in vacuo* at 40° to give an oil, which was chromatographed on a silica-gel column with petroleum ether/AcOEt 9:1. After evaporation of the solvent, the white powder was recrystallized from (i-Pr)$_2$O to afford **6a** (167 mg), m.p. 110–113°, $[\alpha]_D^{22} = +11.78°$ (c = 0.85, $CHCl_3$). UV: 250 (4.40). IR (KBr): 3315 (NH); 2932*s*, 2875*s*, 1728 (carbamate); 870*w*, 845*m*, 820*w* (peroxide); 742*s*, 684*s* (aromatics). ^{1}H-NMR: see *Table 1.* MS (CI; NH_3): 404 ($M^+ + 1$). Anal. calc. for $C_{22}H_{29}NO_6$ (403.48): C 65.49, H 7.24, N 3.47; found: C 65.34, H 7.85, N 3.93.

*Dihydroqinghaosu-*p*-nitrobenzenecarbamate* (= *3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12a-dodecahydro-3β,6α,3β-trimethylpyrano[4,3-j][1,2]benzodioxepin-10α-yl* p*-Nitrobenzenecarbamate;* **6b**). A solution of **2** (142 mg, 0.5 mmol) in dry CH_2Cl_2 (10 ml) was reacted with *p*-nitrophenyl isocyanate (123 mg, 0.75 mmol) as above. Chromatography on silica gel with petroleum ether/AcOEt 9:1 afforded **6b** (120 mg) as a white powder, $[\alpha]_D^{23} = +5.31°$ (c = 1.4, $CHCl_3$). IR (KBr): 3300 (NH); 2925*s*, 2870*s;* 1742 (carbamate); 1540*s*, 1330*s* (NO_2); 845 (peroxide); 740*s*, 680*s* (aromatic). UV: 312 (4.26). ^{1}H-NMR: see *Table 1.*[3]) MS (CI; NH_3): 449 ($M^+ + 1$).

Methyl Artesunate (= *3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12a-dodecahydro-3β,6α,9β-trimethylpyrano[4,3-j][1,2]benzodioxepin-10α-yl Methyl Butanedioate;* **7b**). To a solution of artesunic acid (**7a**; 192 mg, 0.5 mmol) in CH_2Cl_2 (1 ml) was added a freshly prepared solution of CH_2N_2 in Et_2O. Evaporation after 30 min gave **7b** (199 mg) as an oil, $[\alpha]_D^{26.5} = +12.2°$ (c = 1.4, $CHCl_3$). IR ($CHCl_3$): 2932*s*, 1738 (ester), 1008*s*. ^{1}H-NMR: see *Table 1.* MS (CI; NH_3): 399 ($M^+ + 1$).

p*-Nitrobenzyl Artesunate* (*-3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12a-dodecahydro-3β,6α,9β-trimethylpyrano[4,3-j][1,2]benzodioxepin-10α-yl* p*-Nitrobenzyl Butanedioate;* **7c**). To a solution of **7a** (76.8 mg, 0.2 mmol) in CH_2Cl_2 (1 ml) was added a 0.1 M solution of *O*-(*p*-nitrobenzyl)-*N,N'*-diisopropylisourea in CH_2Cl_2 (2

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[3]) The *m*-nitrobenzenecarbonate (m.p. 143–145°; UV: 242 (4.09)) and the *o*-nitrobenzenecarbamate (m.p. 157–159°; UV: 242 (4.06)) were similarly prepared from **2** and *m*-nitrophenyl isocyanate and *o*-nitrophenyl isocyanate, respectively.

ml of '*p*-nitrobenzyl 8' reagent; 0.2 mmol). The mixture was heated at 86° for 24 h, filtered, and evaporated to dryness *in vacuo* to leave an oil. Chromatography on silica gel with petroleum ether/AcOEt 6:4 afforded **7c** (103 mg) as an oil, $[\alpha]_D^{26} = +6.49°$ ($c = 1.3$, $CHCl_3$). UV: 268 (4.04). IR ($CHCl_3$): 2932*m*, 1742*s* (ester), 1713*s*, 1365*s* (NO_2), 1145*s*, 1005*s*, 900 (peroxide). ^{1}H-NMR: see *Table 1*. MS (CI; NH_3): 520 ($M^+ + 1$).

*Dihydroqinghaosu-*p*-Nitrobenzoate (3α,12α-Epoxy-3,4,5,5aα,6,7,8,8aα,9,10,12β,12a-dodecahydro-3β,6α,9β-trimethylpyrano[4,3-j][1,2]benzodioxepin-10α-yl* p*-Nitrobenzoate; **8**). To a solution of dihydroqinghaosu (**2**); 142 mg, 0.5 mmol) in dry CH_2Cl_2 (10 ml) was added *p*-nitrobenzoic acid (91.8 mg, 0.55 mmol) and 4-(dimethylamino)pyridine (6.7 mg). After cooling to 0°, DCC (113.3 mg, 0.55 mmol) was added and the mixture stirred for 16 h at r.t. The mixture was filtered, and the filtrate washed with H_2O (2 × 10 ml), dried (Na_2SO_4), and evaporated to give a light yellow residue, which was chromatographed on a silica-gel column with petroleum ether/AcOEt 9:1 to afford **8** as a white powder, $[\alpha]_D^{27.5} = +20.36°$ ($c = 1.2$, $CHCl_3$). UV: 261 (4.28). IR ($CHCl_3$): 2926*s*, 1735*s* (ester), 1515*m*, 1342*s* (NO_2); 1002*s*, 863*w* (peroxide). ^{1}H-NMR: see *Table 1*. MS (CI; NH_3): 433 ($M^+ + 1$).

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